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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,772	12/20/2000	Peter Francis Joseph O'Hare	5759-56969	4403

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EXAMINER
HUFF, SHEELA JITENDRA

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 09/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/747,772	O'HARE ET AL.	
	Examiner	Art Unit	
	Sheela J Huff	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *7,8,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-6 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that claims 9-16 were pending and not part of the restriction requirement. In view of this the revised restriction requirement is as follows

Group I, claims 1-6, 9-13 and 16

Group II, claims 7 and 14

Group III, claims 8 and 15.

Claims 1-6, 9-13 and 16 are currently under consideration and claims 7-8 and 14-15 are withdrawn from consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on 12/24/99. It is noted, however, that applicant has not filed a certified copy of the UK 9930519.5 document application as required by 35 U.S.C. 119(b).

Sequence listing

In order to fully comply with the sequence rules, applicant needs to insert SEQ ID Nos. to the sequences found on pages 11, 13, 15 and 16 of the specification.

Information Disclosure Statement

The IDS filed 7/30/01 has been considered and an initialed copy of the PTO-1449 in enclosed.

Claim Rejections - 35 USC § 112

Claims 1-6, 9-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro use of conjugates comprising either the fusion protein or the nucleic acids encoding the protein and the in vivo use of the fusion protein of the claimed invention, does not reasonably provide enablement for in vivo use of the nucleic acid encoding said protein or the use of aggregated compositions in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's claims are directed to the in vitro and in vivo uses of fusion proteins and nucleic acids encoding said proteins. While applicant is enabled for the in vitro uses and the in vivo used of the fusion protein, applicant is not enabled for the in vivo use of the nucleic acids encoding said fusion protein (ie gene therapy).

For gene therapy in general, the "Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy", made in December of 1995 summarizes an extensive review by a panel of experts in the field of *in vivo* gene therapy. While the entire report will not be quoted herein, reference to representative conclusions on pages 1 and 2, paragraphs numbered as 2, 6, and 7, is illustrative (applicant is referred to the entirety of the cited report):

> 2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more that 100 Recombinant DNA Advisory Committee (RAC)- approved protocols.
>
> 6. Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance of qualitative rather that quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints. The impression of the Panel is that only a minority of clinical studies, illustrated by some gene marking experiments, have been designed to yield useful basic information.
>
> 7. Overselling of the results of laboratory and clinical studies by investigators and their sponsors--be they academic, federal, or industrial--has led to the mistaken and widespread perception that gene therapy is further developed and more successful than it actually is. Such inaccurate portrayals threaten confidence in the integrity of the field and may ultimately hinder progress toward successful application of gene therapy to human disease.

Thus, the garnering of expression of genes when placed in the *in vivo* environment was at the time of the claimed invention and continuing at least until December of 1995, considered highly unpredictable. In light of the fact that the only disclosed use of the claimed cells is for therapeutic purposes and the specification fails to provide any evidence or guidance in regard to overcoming the difficulties found in the practice of gene therapy, it is maintained that the specification fails to provide an enabling disclosure for how to use the claimed invention.

Several articles also describe the state of the art in nucleic acids involving VP22 fusions. Murphy et al, Gene Therapy vol. 6 p. 4-5 (1/1999) states that "although the VP22 system is clearly an exciting addition to current gene therapy strategies, nuclear localization of the imported fusion protein may limit its potential for treating disorders of cytoplasmic or plasma membrane origin. A further consideration must be the

continuous supply of VP22 fusion protein from tranduced cells, which may be limited by the immunogenicity of the transgene products and of VP22 it self." (see page 5). The articles goes on to say that "an additional concern stems from out ignorance of the function of VP22 in the viral like cycle" and "in summary, VP22-mediated delivery of transgene products may be a promising strategy for successful gene therapy". Fernandez et al Nature Biotechnology vol. 16 p. 418 (5/1998) discusses a multitude of issues involving gene therapy of VP22 systems. See page 419, first and second columns. A few of the issues are re-iterated here, but all of the issues discussed in the article apply. "One important issue is that lack of evidence that VP22 fusions expressed in *E. Coli* are competent for uptake by eukaryotic cells" and the reference goes on to state that more detailed answers are need to many questions such as "can the fusion proteins reach cell surfaces in tissue samples?" and "How long do they take to get in?".

With respect to aggregated compositions, it is apparent that applicant is claiming to broadly. In claim 4, applicant claims that **any** oligonucleotide or polynucletoide can be used in the aggregated composition. It is not clear what the function of these nucleotide sequences in the aggregate is and it is not clear if certain lengths are required for aggregation, do the sequences need to encode for a protein?

In view of the unpredictability and the state of the art described above, and this view of the lack of in vivo working examples, it is the Examiner's position that undue experimentation would be required by one skilled in the art to use the claimed invention.

Claims 1-6, 9-13 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. In claims 1 and 9, applicant uses the work "commonly". This term is vague and indefinite because what is common now will mostly be different from what is common 5-10 years from now.

b. In claim 12, it is not clear what is meant by "Acf".

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hare et al (WO 98/32866) in view of Dilber et al Gene Therapy vol. 6 p. 12 (1/1999) and applicant's admission on pages 3 lines 14-20, page 8, lines 1-10 .

O'Hare et al discloses coupled peptides and fusion proteins for intracellular transport and these comprise the transport function of herpesviral VP22 or a homologue thereof and another protein sequence, which can be a cell cycle control protein (see abstract and page 5, lines 9+). The cell cycle protein can be p53, and cyclin-dependent kinase inhibitors such as p16, p21 and p27 (see page 2 and 9). The VP22 coupled products can be used to induce cell death and apoptosis (page 9 bottom and page 13, lines 4-5).

The only differences between the instant invention and the reference is that combination of the coupled protein with an agent to stimulate cell death and the formation of aggregates.

Dilber et al uses the same VP22 as an in vivo delivery system for thymidine kinase (a suicide protein) and combine the use of their coupled protein with a cancer drug, ganclciovir (see abstract).

On page 3 of the specification, applicant admits that a variety of different proteins that regulate cell cycle progression are known.

On page 8 of the specification, applicant admits that oligonucletoides involved in aggregation are known.

In view of the clear suggestion in the primary reference to use the coupled VP22 protein to regulate apoptosis and in view of the fact that it is known in the art that VP22-

thymidine kinase can used successfully used in vivo, it would have been obvious to one of ordinary skill in the art to the coupled VP22 proteins in vivo with the expected benefits of treating apoptosis. In view of Dilber et al combining the coupled VP22 with another cancer drug that is well known in the art, it would have obvious to one of ordinary skill in the art at the time of applicant's invention to combine the use of known cancer drugs with the coupled VP22. Additionally, it is obvious to "combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose (MPEP 2144.06). Since applicant admits that the formation of aggregates in known, it would have been obvious to one of ordinary skill in the art to form aggregates and to administer them.

Claims 11-13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hare et al (WO 98/32866) in view of Dilber et al Gene Therapy vol. 6 p. 12 (1/1999) and applicant's admission on pages 3 lines 14-20, page 8, lines 1-10 and page 5, lines 16-21 and Dalton et al, J. Clin. Oncol. Vol. 7 p. 415 (1989).

O'Hare et al, Dilber et al, and applicant's admission on pages 3 and 8 have been discussed above.

The only difference between the instant invention and the combined references is the use of an agent that can prevent export from the cell.

On page 5 of the specification, applicant admits inhibitors of proteins which export DNA damaging agents are known and these include the ones recited in the claims. Furthermore, Dalton et al show that the addition of verapamil along with

chemotherapy partially circumvented the drug resistance problem. Verapamil is a P-glycoprotein (which is a multi-drug resistant (MDR) protein) inhibitor (see abstract).

Thus, in view of the known use of an inhibitor of MDR in combination with chemotherapeutics, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the inhibitor or any known inhibitor to overcome drug resistance.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 703-305-7866. The examiner can normally be reached on T,Th 6am-12pm and alternate Mondays 6am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Sheela J Huff
Primary Examiner
Art Unit 1642

sjh
September 19, 2002